REMARKS

Claims 1, 3-5, 16-20, 22-27, 29-32, 34 and 35 are presently pending. Of these, Claims 16-20, 22 and 23 are withdrawn from consideration. Amendments to Claims 1, 3, 4 and 32 and new Claim 35 are discussed below. No new matter has been added herewith. The following addresses the substance of the Office Action.

Written Description

Claim 32 was rejected under 35 U.S.C. § 112, first paragraph as containing new matter. The Examiner noted that the specification does not disclose eluting plasminogen and fibrinogen together. In addition the Examiner pointed out that the specification discloses that plasminogen was eluted with buffers comprising a salt of phosphate and chloride and that fibrinogen was eluted with buffers comprising a salt of citrate and chloride.

The Applicant has amended Claim 32 to recite that the buffers for eluting plasminogen comprise a salt of phosphate and chloride and new Claim 35 recites that the buffers for eluting fibrinogen comprise a salt of citrate and chloride. Accordingly, the amended claims do not contain new matter and the Applicant respectfully requests that the rejection be withdrawn.

Indefiniteness

Claims 1, 3 and 24-33 were rejected under 35 U.S.C. § 112, second paragraph as being indefinite. In particular, the relative terms "low concentration," "higher concentration," "reduced pH compared to loading solution" and "reduced ionic strength compared to loading solution" were found to be unclear because the metes and bounds of what would constitute these conditions cannot be determined. In response, the terms "low concentration" and "higher concentration" have now been replaced by suitable values of concentrations for the chelating agents. Furthermore, the terms "reduced pH compared to loading solution" and "reduced ionic strength compared to loading solution" have been deleted.

The Examiner asserted that not all amino acids are competitive chelating compounds. However, the Applicant believes that the Examiner's assertion is misplaced. In this regard, the Examiner has not supported this assertion in any way, and merely indicated that the application as filed does not provide any embodiment examples demonstrating that all amino acids can be used. In the context of the present application, the term "competitive chelating compound" is used in

relation to the elution of bound proteins from immobilized metal ion affinity chromatography (IMAC) matrices by displacement. Referring to the Specification as filed at page 6, lines 34-36, the specification discloses that suitable chelating agents for the elution of plasminogen include amino acids. Certain amino acids are exemplified, but no amino acids are excluded. Similarly, referring to page 7, lines 14-17, preferred chelating compounds for the elution of fibrinogen are amino acids. Again, certain amino acids are exemplified, but no amino acids are excluded.

Moreover, in response to the previous Office Action, the Applicant drew the Examiner's attention to Example 14 of U.S. Patent No. 5,445,958 (submitted with an Information Disclosure Statement on September 11, 2009), which shows that other proteins can be eluted from IMAC matrices using a variety of non-polar, polar uncharged, polar negatively charged and polar positively charged amino acids, which represent the various amino acid chemistries. In the absence of any substantiated reason why amino acids in general can not also be used in the present invention, the Applicant believes that, in addition to being supported by the specification, based on published reports, e.g., U.S. Patent No. 5,445,958, one of ordinary skill in the art would know that amino acids as a group are suitable competitive chelating compounds for the elution of fibrinogen or plasminogen from an IMAC matrix.

In view of the amendments to the claims and the preceding remarks, the claims are believed to be in compliance with the requirements of 35 U.S.C. § 112, second paragraph and the Applicant respectfully requests that the rejection be withdrawn.

Obviousness

Claims 1, 3-5, 24-26 and 31-33 were rejected under 35 U.S.C. § 103(a) as being unpatentable over WO 90/12803 in view of Chaga et al. (2001 *Biochem Biophys Methods* **49**:313-334) and WO 95/25748. WO 90/12803 is an equivalent of U.S. Patent No. 5,169,936. which the Examiner cited previously. WO 90/12803 discloses the use of IMAC for the purification of proteins from solutions containing contaminants. In particular, the examples of WO 90/12803 disclose the use of IMAC for the purification of recombinant soluble T4 (rsT4). The final paragraph of the reference indicates that the process disclosed therein may be used to purify other proteins, such as *inter alia* human fibrinogen (see page 21, line 14). Chaga et al. teaches that IMAC columns may be eluted by decreasing pH or by use of a competitive molecule such as imidazole, which competes for metal ions immobilized on the column. The third reference

cited, WO 95/25748, discloses concentrating fibrinogen by ultrafiltration to a desired concentration prior to lyophilization. On the basis of these references, the Examiner concluded that there would have been a reasonable expectation of success in combining the three references to arrive at the presently claimed methods.

However, the Applicant notes that the primary reference, WO 90/12803, is merely speculative with regard to the ability of the IMAC technique to separate fibrinogen from a complex mixture. In this regard, referring to the paragraph that spans pages 20-21 of WO 90/12803, fibrinogen is listed among a long list other possible proteins that allegedly may be isolated by the process of WO 90/12803, but no data is provided for isolation of fibrinogen. Furthermore, WO 90/12803 provides no indication that IMAC may be used for the separation and purification of both fibrinogen and/or plasminogen from a solution containing a complex mixture. It is important to note that WO 90/12803 does not provide any disclosure of plasminogen. The paragraph that spans pages 20-21 of WO 90/12803 describes in general terms that the process of WO 90/12803 can be used to separate numerous types of proteins, including plasminogen activator (page 21, line 11). However, plasminogen activator is a completely different protein to plasminogen and cannot be expected to have properties similar to plasminogen when loaded onto a metal ion affinity chromatography matrix.

It appears that the Examiner based the present rejection on the assumption that it was common knowledge that fibrinogen and plasminogen could both be separated from a complex protein solution using metal ion affinity chromatography. However, the Examiner has not indicated from which document this is known, or why this would be obvious from any of the cited art. As noted above, WO 90/12803 provides no indication that IMAC may be used in the separation of fibrinogen from other proteins, much less the independent separation of fibrinogen and plasminogen from a more complex protein solution. Thus, it would be incorrect to conclude that the invention only lies in devising suitable conditions in order to effectively achieve separation of fibrinogen and plasminogen.

No Reasonable Expectation of Success

The Supreme Court, in *KSR International Co v. Teleflex Inc.*, reaffirmed that a rationale to support a conclusion of obviousness is that an invention was "obvious to try"- choosing from a finite number of identified, predictable solutions, as long as there was with a reasonable

expectation of success. In the present case, the Examiner has not made a proper *prima facie* case of obviousness because the combination of cited references would not provide one of ordinary skill in the art with the required reasonable expectation of success. As explained in M.P.E.P. § 2143.02, references cited must provide some expectation of success in the claimed combination to sustain an obviousness rejection. At least some degree of predictability is required and Applicant may present evidence showing there was no reasonable expectation of success.

Although the Applicant appreciates that opinions of the International Bureau are not binding on the USPTO, the Applicant would like to draw the Examiner's attention to the conclusions of the International Preliminary Examination Authority in Section V-3 of the International Preliminary Examination Report (copy of IPER, submitted herewith) of the corresponding International application, where it is stated:

> "None of the known prior art documents discloses or renders obvious that fibrinogen could be separated from plasminogen by means of metal ion affinity chromatography (IMAC)…"

The IPER goes on to state:

> "It would appear to be generally acknowledged that the binding properties of proteins to affinity media cannot *a priori* be reasonably predicted".

In support of the conclusion reached by the International Preliminary Examination Authority, the Applicant submits herewith a copy of Applied BioSystems Inc. user instructions for IMAC POROS® 50MC Chromatography Media, dated 2005. Section 4 on page 4 of this document indicates that:

> "because metal chelate chromatography is not as well developed as more traditional chromatography mode such as ion-exchange or reversed-phase, it is virtually impossible to predict retention behaviour. As a result, conditions for binding an elution must be developed by trial and error". [Emphasis added]

Thus, even well after the filing date of the present application, the manufacturers of IMAC columns acknowledged that it is not possible to reasonably predict which proteins may efficiently be separated using the IMAC technique. Due to the fact that the binding properties of proteins to affinity media cannot *a priori* be reasonably predicted, there was no reasonable expectation that the presently claimed methods would be successful.

The present invention lies in the recognition that IMAC may be used to effectively and efficiently separate plasminogen from fibrinogen. Thus far, the Examiner has not substantiated

why any of the cited documents provide a clear teaching that it would have been obvious to separate plasminogen and fibrinogen using IMAC. Instead, the Examiner appears to conclude that this was common knowledge, and asserts that the conditions used in the presently amended claims were obvious based on what was commonly known in the art. The Applicant agrees that, if it had been common knowledge that fibrinogen and plasminogen could be efficiently separated using IMAC, it would have been a matter of routine experimentation to devise suitable conditions in order to optimize the separation process. However, the inventive aspect of the presently claimed methods, which lies in the discovery that fibrinogen and/or plasminogen can be efficiently separated from each other or from a complex solution using IMAC, was previously unknown. The extensive teaching contained in the application as filed provides the skilled person with enough information such that suitable conditions (chelating compounds, pH, ionic strength) in order to effectively elute either the plasminogen or the fibrinogen could be developed without undue burden, once the skilled person knows that this is possible.

In view of the foregoing remarks, the Applicant respectfully requests that the rejection be withdrawn.

Claim 27 was rejected under 35 U.S.C. § 103(a) as being unpatentable over WO 90/12803 in view of Chaga et al. (*supra*), WO 95/25748 and WO 96/17631. Claim 27 includes the further step of subjection lyophilized fibrinogen to dry heat treatment and WO 96/17631 teaches that lyophilized fibrinogen is heat treated. However, the reference does not provide any additional information that would have provided a reasonable expectation of success for the presently claimed methods, as discussed above. Thus, the Applicant respectfully requests that this rejection also be withdrawn.

No Disclaimers or Disavowals

Although the present communication may include alterations to the application or claims, or characterizations of claim scope or referenced art, Applicant is not conceding in this application that previously pending claims are not patentable over the cited references. Rather, any alterations or characterizations are being made to facilitate expeditious prosecution of this application. Applicant reserves the right to pursue at a later date any previously pending or other broader or narrower claims that capture any subject matter supported by the present disclosure,

including subject matter found to be specifically disclaimed herein or by any prior prosecution. Accordingly, reviewers of this or any parent, child or related prosecution history shall not reasonably infer that Applicant has made any disclaimers or disavowals of any subject matter supported by the present application.

Co-Pending Applications of Assignee

Applicant wishes to draw the Examiner's attention to the following co-pending applications of the present application's assignee.

Docket No.	Serial No.	Title	Filed
FDEHN7.001APC	10/520457	PROCESS FOR PRODUCING A VIRUS-INACTIVATED THROMBIN PREPARATION	30-Nov-2005

CONCLUSION

In view of Applicants' amendments to the Claims and the foregoing Remarks, it is respectfully submitted that the present application is in condition for allowance. Should the Examiner have any remaining concerns which might prevent the prompt allowance of the application, the Examiner is respectfully invited to contact the undersigned at the telephone number appearing below.

Please charge any additional fees, including any fees for additional extension of time, or credit overpayment to Deposit Account No. 11-1410.

Respectfully submitted,

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Dated: February 25, 2010

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